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(54) Formulation.

(57) Pharmaceutical formulations for the parenteral administration of 1-isobutyl-1H-imidazo[4,5-c]quinolin-4-amine or 1-(2-hydroxy-2-methylpropyl)-1-H-imidazo[4,5-c] quinolin-4-amine are described.

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FORMULATION

BACKGROUND OF THE INVENTION

Field of the Invention

This invention pertains to pharmaceutical formulations suitable for the parenteral administration of drugs. More particularly, it pertains to solutions containing 1-isobutyl-1H-imidazo[4,5-c]quinolin-4-amine or 1-(2-hydroxy -2-methylpropyl)-1-H-imidazo[4,5-c]quinolin-4-amine which are suitable for parenteral administration.

Description of the Related Art

The compound 1-isobutyl-1H-imidazo[4,5-c]quinolin-4-amine and pharmaceutically acceptable acid addition salts such as the hydrochloride salt are disclosed in U.S. Patent No. 4,689,338 and described therein as an antiviral agent and as an interferon inducer. A variety of formulations for topical administration are described but a formulation suitable for parenteral administration of this compound is not disclosed. U.S Patent No. 4,689,338 also similarly discloses the compound 1-(2-hydroxy-2-methylpropyl)-1H-imidazo[4,5-c]quinolin-4-amine.

U. S. Patent Nos. 4,640,930, 4,652,561 and 4,808,580 describe parenteral solutions containing (+/-)-cis-3-(acetyloxy)-2,3-dihydro-5-[2-(dimethylamino) ethyl]-2-(4-methoxyphenyl)naphtho[1,8-bc]-1,5-thiazocin-4-(5H)-one hydrochloride, (+/-)-cis-3-(acetyloxy)-2,3-dihydro-2-(4-methoxyphenyl)-5-[2-(dimethylamino)ethyl]-naptho[1,2-b]-1-4-thiazepin-4(5H)-one hydrochloride, and cis-rac-2,3-dihydro-3-hydroxy-5-[2-(dimethylamino)ethyl]2-(4- methoxyphenyl)-naphtho[2,1-2b][1,4-thiazepin-4(5H)-one hydrochloride, respectively in benzyl alcohol, sorbitol, hydrochloric acid, sodium hydroxide and water.

SUMMARY OF THE INVENTION

The present invention provides an aqueous solution suitable for the parenteral administration comprising 1-isobutyl-1H-imidazo[4,5-c]quinolin-4-amine or 1-(2-hydroxy-2-methylpropyl)-1H-imidazo[4,5-c]quinolin-4-amine dissolved in an aqueous acid, the acid being selected from the group consisting of hydrochloric acid, lactic acid, acetic acid, aspartic acid and a mixture of two or more of the foregoing, and further comprising a tonicity adjuster of a type and present in an amount such that the osmolality of said solution is between about 235 and 335 mOsm/kg, the solution being further characterized in that it has a pH of between about 2 and 6.

A solution of the invention can be used for the parenteral administration of 1-isobutyl-1H-imidazo[4,5-c]-quinolin-4-amine or 1-(2-hydroxy-2-methylpropyl)-1H-imidazo [4,5-c]quinolin-4-amine. The solution may be administered by intramuscular injection, intradermal injection, subcutaneous injection or intravenous injection.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides aqueous solutions suitable for parenteral administration that contain 1-isobutyl-1H-imidazo[4,5-c]quinolin-4-amine or

1-(2-hydroxy-2-methylpropyl)-1-H-imidazo[4,5-c]quinolin-4-amine dissolved in an aqueous acid such as hydrochloric acid, lactic acid, acetic acid, aspartic acid or mixtures thereof.

The compounds 1-isobutyl-1H-imidazo[4,5-c]quinolin-4-amine and 1-(2-hydroxy-2-methylpropyl)-1H-imidazo[4,5-c]- quinolin-4-amine are known antiviral agents that are also known to induce interferon

biosynthesis. They can be prepared using the method disclosed in U.S. Patent No. 4,689,338, the disclosure of which is incorporated herein by reference. The compounds can be used to treat viral infections such as Type I or Type II Herpes simplex infections and genital warts. Furthermore, the fact that the compounds are interferon inducers suggests that they, and therefore solutions containing them, might be useful in the treatment of numerous other diseases, such as rheumatoid arthritis, warts, eczema, hepatitis B, psoriasis, multiple sclerosis, essential thrombocythaemia, and cancer, such as basal cell carcinoma and other neoplastic diseases. The amount of 1-isobutyl-1H-imidazo[4,5-c]quinolin-4-amine or 1-(2-hydroxy-2-methylpropyl)-1H-imidazo[4,5-c]quinolin-4-amine present in a solution of the invention will be an amount effective to treat the targeted disease state, to prevent recurrence of such a disease or to promote immunity against such a disease. The amount is preferably about 0.01 milligrams to about 15 milligrams, more preferably about 4 milligrams to about 12 milligrams, per milliliter of the solution.

An acid selected from the group consisting of hydrochloric acid, lactic acid, acetic acid, aspartic acid or mixtures thereof is incorporated into a solution of the invention. The currently preferred acid is hydrochloric acid. The acid will be present in amount sufficient to keep the 1-isobutyl-1H-imidazo[4,5-c]quinolin-4-amine or 1-(2-hydroxy-2-methylpropyl)-1H-imidazo[4,5-c]quinolin-4-amine in solution. The acid will generally be present in an amount of between 0.5 moles and 20 moles of acid per mole of 1-isobutyl-1H-imidazo[4,5-c]-quinolin-4-amine or 1-(2-hydroxy-2-methylpropyl)-1-H-imidazo[4,5-c]quinolin-4-amine. Preferably the molar ratio of acid to 1-isobutyl-1H-imidazo[4,5-c]quinolin-4-amine or 1-(2-hydroxy-2-methylpropyl)-1H-imidazo-[4,5-c]quinolin-4-amine will be between 1/1 and 4/1.

The acid may be provided through the presence of the respective acid-addition salt of 1-isobutyl-1H-imidazo[4,5-c]-quinolin-4-amine or 1-(2-hydroxy-2-methylpropyl)-1H-imidazo [4,5-c]quinolin-4-amine. For example, an aqueous hydrochloric acid solution may be obtained by using 1-isobutyl-1H-imidazo[4,5-c]-quinolin-4-amine hydrochloride in place of the free base. Additional acid such as hydrochloric acid may also be added even when an acid-addition salt of 1-isobutyl-1H-imidazo[4,5-c]quinolin-4-amine or 1-(2-hydroxy-2-methylpropyl)-1H-imidazo[4,5-c]-quinolin-4-amine is employed.

In order to minimize pain on injection and tissue irritation it is desirable that the pH of the solutions of the invention not be below 2. The pH of the solution will generally be between about 2 and 6. Optionally, a solution of the invention may further comprise a base to provide the desired pH. It is preferred that the pH be between about 2.5 and 4.5. The currently preferred base is sodium hydroxide. Care must be taken in adjusting the pH of the solutions so that the 1-isobutyl-1H-imidazo[4,5-c]quinolin-4-amine or 1-(2-hydroxy-2-methylpropyl)-1H-imidazo[4,5-c]quinolin-4-amine does not precipitate.

An additional factor affecting pain on injection and tissue irritation at the injection site is the osmoticity of the solution. It is preferred that the solution be isotonic with serum or isoosmotic with 0.9% sodium chloride. A quantitative term used to state osmotic properties is the osmol. An osmol is defined as the weight in grams of a solute, existing in a solution as molecules (and/or ions, macromolecules, aggregates, etc), that is osmotically equivalent to the gram-molecular-weight of an ideally behaving nonelectrolyte. A milliosmol, abbreviated mOsm, is the weight stated in milligrams. A solution has an osmolal concentration of one when it contains one osmol of solute per kilogram of water. A solution has an osmolality of n when it contains n osmols per kilogram of water. Further discussion of tonicity, osmoticity and isomolality may be found in Chapter 80 in the Seventeenth Edition of Remington's Pharmaceutical Sciences, incorporated herein by reference. A range of values from about 275 mOsm/kg to about 305 mOosm/kg has been reported for serum osmolality. Accordingly, preferred solutions of the invention may further comprise a tonicity adjuster present in an amount such that the osmolality of the solution is between about 235 mOsm/kg to about 335 mOsm/kg and most preferably between about 270 mOsm/kg and about 310 mOsm/kg. The osmolality of a solution is determined using the test method described below. Care must be taken in the choice of tonicity adjusters so that the 1-isobutyl-1H-imidazo[4,5-c]quinolin-4-amine or 1-(2-hydroxy-2-methylpropyl)-1H-imidazo[4,5-c]quinolin-4-amine stays in solution. The currently preferred tonicity adjusters are sorbitol and glycerin. When sorbitol is used it will generally be present in an amount of about 40 milligrams per milliliter of solution.

A solution of the invention can be prepared by combining the acid with a major portion of the water to be used in the formulation, adding the 1-isobutyl-1H-imidazo[4,5-c]quinolin-4-amine or 1-(2-hydroxy-2-methylpropyl)-1H-imidazo[4,5-c]quinolin-4-amine to this solution and stirring until all material is in solution. The sorbitol may then be added and stirring continued until dissolution is complete. The pH of the solution is then measured and a base may be added to adjust the pH if desired. A sufficient quantity (qs) of water is then added to bring the solution to the desired total volume. The bulk solution may then be filtered through a 0.2 micron filter, heat sealed into USP Type I glass ampules and autoclaved.

Preferred solutions of the invention may be stored at room temperature for a period of at least 30 days without precipitation or degradation of the active ingredient. Most preferred solutions exhibit such stability

for a period of at least one year.

The following test methods have been employed in the examples which thereafter follow.

Osmolality Determination

Osmolality was determined using a Molecular Weight Apparatus, Model 233 available from Wescan Instruments. A series of 5 standard solutions of sodium chloride in water having known osmolality values were prepared. Microvolt readings for each standard were taken on the Molecular Weight Apparatus. Using linear regression analysis, the readings together with the known osmolality values were used to determine the values of m and b in the equation below.

instrument reading = m(osmolality in mOsm/kg) + b

The values of m and b in conjunction with the instrument readings for the solutions of the invention allow the osmolality values of the solutions to be calculated. The readings for the standards and the solutions of the invention were preferably taken on the same day to insure accuracy. At least three readings were taken for each standard and solution and the average was used in the above calculations.

The above method is to be used for purposes of construing the claims, with the number of readings being taken being five.

Determination of 1-Isobutyl-1H-imidazo[4,5-c]quinolin-4-amine Content

The solutions used in the stability studies were analyzed for 1-isobutyl-1H-imidazo[4,5-c]quinolin-4-amine content by conventional high pressure liquid chromatography as follows:

A 15 centimeter by 4 millimeter column containing Zorbax® C_8 (an octylsilane available from E. I. Dupont de Nemours & Company), 5 micron particle size, was used. The mobile phase was 35 percent acetonitrile/65 percent water (volume/volume) containing 0.2 percent tetramethylammonium hydroxide and 0.2 percent 1-dodecanesulfonate sodium, with the pH of the mobile phase adjusted to 2.0 with phosphoric acid. The flow rate was 2.5 ml per minute. Ultraviolet detection at 254 nanometers was used.

The following examples are provided to illustrate the invention, but are not intended to be limiting thereof.

Example 1

A mixture of 0.20 g 1-isobutyl-1H-imidazo[4,5-c]-quinolin-4-amine, 0.20 g of 85% lactic acid, 0.344 g of glycerin and 19.256 g of water was placed in a glass vial and shaken until all material was dissolved. The resulting solution of the invention had a pH of 3.59 and the osmolality was 279 mOsm/Kg. No drug precipitated on storage at room temperature for 30 days.

Example 2

A mixture of 0.20 g of 1-isobutyl-1H-imidazo[4,5-c]-quinolin-4-amine, 0.20 g of 85% lactic acid, 1.10 g of sorbitol 50% (prepared by combining 29 ml of water and 71 ml of sorbitol 70%) and 18.50 g of water was placed in a glass vial and shaken until all material was dissolved. The resulting solution of the invention had a pH of 3.58 and the osmolality was 271 mOsm/Kg. No drug precipitated on storage at room temperature for 30 days.

Example 3

A mixture of 0.050 g of 1-isobutyl-1H-imidazo[4,5-c]quinolin-4-amine, 22 ml of 0.1N HCl and 15 ml of water was placed in a beaker and stirred until all material was in solution. To this solution was added 2.0 g

of sorbitol and stirring was continued until the sorbitol was dissolved. The solution was transferred to a 50 ml volumetric flask. The pH of the solution was adjusted with 2N sodium hydroxide then the flask was filled to the mark with water. The compositon of the final formulation of the invention is shown in Table 1.

Examples 4-6

Using the general method of Example 3, the formulations of the invention shown in Table 1 were prepared.

Table 1

	Ex. 3	Ex. 4	Ex. 5	Ex. 6
1-Isobutyl-1H-imidazo-[4,5-c]quinolin-4-amine (mg/ml)	1.0	2.5	5.0	10.0
Sorbitol (mg/ml)	40	40	40	40
0.1H HCl (ml/ml)	0.44	0.44	0.44	0.44
2N NaOH qs to pH	3.5	3.2	3.2	3.2
Water qs to 1 ml Osmolality (mOsm/Kg)	303	307	294	284

Example 7

To a 500 ml volumetric flask was added 5.00 g of 1-isobutyl-1H-imidazo[4,5-c]quinolin-4-amine, 200 ml of 0.1N hydrochloric acid and 230 ml of sterile water. The flask was sonicated for 50 minutes then an additional 20 ml of 0.1N hydrochloric acid was added and sonicating was continued for 20 minutes. The flask was heated on a steam bath to 62 °C then sonicated for 30 minutes. A small amount of insoluble material remained which was removed during the filtration step below. The flask was allowed to cool to 25 °C before 20.0 g of sorbitol was added. The sorbitol was mixed by inverting the flask by hand until the sorbitol had dissolved. The pH was adjusted by adding 1.35 ml of 2N sodium hydroxide. A quantity of sterile water sufficient to bring the final volume to 500 ml was added. The formulation was filtered through a 0.2 micron filter then heat sealed in 2 ml Type I clear glass ampules. The ampules were autoclaved at 121 °C for 30 minutes. The ampules were divided into groups and stored under a variety of conditions. At selected time points ampules were evaluated for color and clarity of solution, pH and 1-isobutyl-1H-imidazo-[4,5-c]quinolin-4-amine content. The results relating to this formulation of this invention are summarized in Table 2.

Table 2

Storage Condition	Time	pH	1-Isobutyl-1H-imidazo[4,5-c]-quinolin-4-amine content (mg/ml)
initial		3.1	9.94
50° C	4 weeks	3.6	9.93
50° C	8 weeks	3.4	10.5
50°	12 weeks	3.5	9.94
40° C	4 weeks	3.6	9.88
40° C	8 weeks	3.5	10.3
40° C	12 weeks	3.4	9.92
40° C	6 months	3.2	10.8
30° C	4 weeks	3.5	9.92
30° C	12 weeks	3.4	9.95
30° C	6 months	3.3	10.6
30° C	9 months	3.2	10.5
30° C	12 months	3.4	10.1
20° C*	2 weeks	3.3	9.81
20° C*	4 weeks	3.5	9.86
20° C*	8 weeks	3.4	10.2
20° C*	12 weeks	3.4	9.95
Freeze-thaw 3 cycles		3.4	9.96

* with 100 foot candle light

Throughout the study, all ampules contained clear, colorless solutions.

Example 8

To a glass carboy was added 0.15 g of 1-isobutyl-1H-imidazo[4,5-c]quinolin-4-amine, 220 ml of 1N hydrochloric acid and 4200 ml of sterile water. The carboy was mixed until all material was dissolved, then 200 g of sorbitol was added and swirled until dissolved. The pH was adjusted by adding 112.1 ml of 2N sodium hydroxide. A sufficient quantity of sterile water was added to bring the total volume of formulation to 5000 ml. The formulation was mixed with a magnetic stir bar then filtered through two 0.22 micron filters. The filtrate was heat sealed into Type I 10 ml clear glass ampules. The ampules were autoclaved at 121° C for 30 minutes. The composition of the final formulation of the invention is shown in Table 3. Stability data is shown in Table 4.

Examples 9-11

Using the general method of Example 8, formulations having the compositions shown in Table 3 were prepared. The stability data is shown in Table 4.

Table 3

	Ex. 8	Ex. 9	Ex. 10	Ex. 11
1-Isobutyl-1H-imidazo-[4,5-c]quinolin-4-amine (mg/ml)	0.03	0.15	0.9	3.0
Sorbitol NF (mg/ml)	40	40	40	40
1N HCl (ml/ml)	0.044	0.044	0.044	0.044
2N NaOH qs to pH	3.1	3.4	3.3	3.5
Sterile water qs to 1 ml				

TABLE 4

Storage Condition	Time	pH	Ex. 8 Content	pH	Ex. 9 Content	pH	Ex. 10 Content	pH	Ex. 11 Content
Initial		3.25	0.0296	3.48	0.150	3.39	0.945	3.60	3.06
50 ° C	4 wk	3.28	0.0302	***		***		3.64	3.05
40 ° C	12 wk	3.33	0.0299	***		***		3.85	3.09
30 ° C	4 wk	3.27	0.0297	3.56	0.151	3.34	0.934	3.7	3.04
30 ° C	12 wk	3.33	0.0299	3.56	0.151	3.46	0.931	3.63	3.04
30 ° C	6 mon	3.28	0.0299	3.57	0.148	3.48	0.919	3.83	2.98
30 ° C	9 mon	3.36	0.0289	3.62	0.146	3.52	0.904	3.82	2.86
20 ° C*	4 wk	3.27	0.0293	3.56	0.150	3.31	0.933	3.7	3.12
20 ° C*	12 wk	3.30	0.0282	3.66	0.148	3.44	0.935	3.61	3.06
20 ° C**	4 wk	3.26	0.0248	3.51	0.144	3.25	0.935	3.8	3.07

Content - amount of 1-isobutyl-1H-imidazo[4,5-c]quinolin-4-amine (mg/ml)

* with 100 foot candle light
** with 1000 foot candle light
*** not available

Example 12

A 6 liter flask was charged with 220.0 ml of 1.0N hydrochloric acid and approximately 4200 ml of sterile water; then 25.0 gram of 1-isobutyl-1H-imidazo[4,5-c]quinolin-4-amine was added and the resulting mixture stirred with a magnetic stir bar until all material was dissolved. To this solution was added 200.0 gram of sorbitol and stirring was continued until the sorbitol was dissolved. The pH of the solution was adjusted to pH 3.32 by adding 62.3 ml of 2N sodium hydroxide. Sterile water was added in a quantity sufficient to bring the total volume to 5.0 liters. The solution was filtered through a 0.22 micron filter then sealed in 2 ml Type I glass ampules. The ampules were autoclaved at 121 ° C for 30 minutes. The composition of the final formulation of the invention is shown in Table 5. Stability data is shown in Table 6.

Example 13

Using the general method of Example 12, the formulation of the invention shown in Table 5 was prepared. The stability data is shown in Table 6.

Table 5

	Example 12	Example 13
1-Isobutyl-1H-imidazo-[4,5-c]quinolin-4-amine (mg/ml)	5.00	10.00
Sorbitol NF (mg/ml)	40	40
1.0N HCl (ml/ml)	0.044	0.044
2N NaOH qs to pH	3.32	3.15
Sterile water qs to 1 ml		

Table 6

		Example 12		Example 13	
Storage Condition	Time	pH	Content	pH	Content
Initial		3.4	4.98	3.2	9.85
50° C	4 weeks	3.1	4.98	3.1	9.77
50° C	12 weeks	3.3	4.99	3.2	9.91
30° C	12 weeks	3.2	5.02	3.1	9.85
20° C*	4 weeks	3.2	4.96	3.1	9.79
20° C*	12 weeks	3.2	4.99	3.1	9.94
20° C**	4 weeks	3.2	4.96	3.1	9.83

Content = amount of 1-isobutyl-1H-imidazo[4,5-c]quinolin-4-amine (mg/ml)

* with 100 foot candle light

** with 1000 foot candle light

Example 14

A mixture of 0.23 g of 1-isobutyl-1H-imidazo [4,5-c]quinolin-4-amine hydrochloride, 0.40 g of glycerin and 19.34 g of sterile water was placed in a glass vial and shaken until all material was dissolved. The resulting solution of the invention had a pH of 4.11 and the osmolality was 280 mOsm/kg.

Example 15

A mixture of 0.23 g of 1-isobutyl-1H-imidazo [4,5-c]quinolin-4-amine hydrochloride, 1.50 g of sorbitol 50% (prepared by combining 29 ml of water and 71 ml of sorbitol 70%) and 18.27 g of sterile water was placed in a glass vial and shaken until all material was dissolved. The resulting solution of the invention had a pH of 4.08 and the osmolality was 298 mOsm/kg.

Example 16

An aqueous solution was prepared from the following ingredients:

1-(2-hydroxy-2-methylpropyl)-1H-imidazo[4,5-c]quinolin-4-amine	0.2g
Lactic acid (85% in water)	0.19g
Sterile water qs to 25 ml	

The pH of the above solution was 3.3.
It is believed that the tonicity of the solution could be modified through inclusion of, for example, sorbitol in an appropriate amount to provide a solution of the invention.

Claims

1. An aqueous solution of 1-isobutyl-1H-imidazo[4,5-c]quinolin-4-amine or 1-(2-hydroxy-2-methylpropyl)-1-H-imidazo[4,5-c]quinolin-4-amine suitable for parenteral administration comprising 1-isobutyl-1H-imidazo-[4,5-c]-quinolin-4-amine or 1-(2-hydroxy-2-methylpropyl)-1H-imidazo[4,5-c]quinolin-4-amine dissolved in an aqueous acid, said acid selected from the group consisting of hydrochloric acid, lactic acid, acetic acid, aspartic acid and a mixture of two or more of the foregoing, and further comprising a tonicity adjuster of a type and present in an amount such that the osmolality of said solution is between about 235 and 335 mOsm/kg, said solution being further characterized in that it has a pH of between about 2 and 6.

2. A solution according to claim 1, wherein 1-isobutyl-1H-imidazo[4,5-c]quinolin-4-amine or 1-(2-hydroxy-2-methylpropyl)-1H-imidazo[4,5-c]quinolin-4-amine is present in an amount effective for the intended therapeutic purpose.

3. A solution according to Claim 1, wherein said acid is hydrochloric acid.

4. A solution according to Claim 3, comprising 1-isobutyl-1H-imidazo[4,5-c]quinolin-4-amine and wherein said hydrochloric acid is provided at least in part by hydrochloric acid present in 1-isobutyl-1H-imidazo[4,5-c]quinolin-4-amine hydrochloride.

5. A solution according to Claim 1, wherein said acid is lactic acid.

6. A solution according to Claim 1, wherein the pH is between about 2.5 and 4.5.

7. A solution according to Claim 1, comprising said 1-isobutyl-1H-imidazo[4,5-c]quinolin-4-amine or 1-(2-hydroxy-2-methylpropyl)-1H-imidazo[4,5-c]quinolin-4-amine in an amount of about 0.01 to 15 milligrams per milliliter of said solution.

8. A solution according to Claim 7, wherein said 1-isobutyl-1H-imidazo[4,5-c]quinolin-4-amine or 1-(2-hydroxy-2-methylpropyl)-1-H-imidazo[4,5-c]quinolin-4-amine is present in an amount of about 4 to 12 milligrams per milliliter of said solution.

9. A solution according to Claim 1, further comprising a base.

10. A solution according to Claim 9, wherein said base is sodium hydroxide.

11. A solution according to Claim 1, wherein said tonicity adjuster is selected from the group consisting of glycerin, sorbitol and dextrose.

12. A solution according to Claim 11, wherein said tonicity adjuster is sorbitol.

13. A solution according to Claim 1, wherein the molar ratio of said acid to said 1-isobutyl-1H-imidazo-[4,5-c]quinolin-4-amine or 1-(2-hydroxy-2-methylpropyl)-1H-imidazo[4,5-c]quinolin-4-amine is between about 0.5/l and 20/1.

14. A solution according to Claim 13, wherein the molar ratio of said acid to said 1-isobutyl-1H-imidazo-[4,5-c]quinolin-4-amine or 1-(2-hydroxy-2-methylpropyl)-1H-imidazo[4,5-c]quinolin-4-amine is between about 1/1 and 4/1.

15. A solution according to Claim 1, wherein the osmolality of said solution is between about 270 and 310 mOsm/kg.

Claims for the following Contracting State:

1. A method of preparing an aqueous solution of 1-isobutyl-1H-imidazo[4,5-c]quinolin-4-amine or 1-(2-hydroxy-2-methylpropyl)-1-H-imidazo[4,5-c]quinolin-4-amine suitable for parenteral administration comprising dissolving 1-isobutyl-1H-imidazo[4,5-c]-quinolin-4-amine or 1-(2-hydroxy-2-methylpropyl)-1H-imidazo-[4,5-c]quinolin-4-amine in an aqueous acid, said acid selected from the group consisting of hydrochloric acid, lactic acid, acetic acid, aspartic acid and a mixture of two or more of the foregoing, and further adding a tonicity adjuster of a type and in an amount such that the osmolality of said solution is between about 235

and 335 mOsm/kg, said solution being adjusted to have a pH of between about 2 and 6.

2. A method according to claim 1, wherein 1-isobutyl-1H-imidazo[4,5-c]quinolin-4-amine or 1-(2-hydroxy-2-methylpropyl)-1H-imidazo[4,5-c]quinolin-4-amine is added in an amount effective for the intended therapeutic purpose.

3. A nethod according to Claim 1, wherein said acid is hydrochloric acid.

4. A method according to Claim 3, comprising 1-isobutyl-1H-imidazo[4,5-c]quinolin-4-amine and wherein said hydrochloric acid is provided at least in part by hydrochloric acid present in 1-isobutyl-1H-imidazo[4,5-c]quinolin-4-amine hydrochloride.

5. A method according to Claim 1, wherein said acid is lactic acid.

6. A method according to Claim 1, wherein the pH is between about 2.5 and 4.5.

7. A method according to Claim 1, comprising said 1-isobutyl-1H-imidazo[4,5-c]quinolin-4-amine or 1-(2-hydroxy-2-methylpropyl)-1H-imidazo[4,5-c]quinolin-4-amine added in an amount of about 0.01 to 15 milligrams per milliliter of said solution.

8. A method according to Claim 7, wherein said 1-isobutyl-1H-imidazo[4,5-c]quinolin-4-amine or 1-(2-hydroxy-2-methylpropyl)-1-H-imidazo[4,5-c]quinolin-4-amine is present in an amount of about 4 to 12 milligrams per milliliter of said solution.

9. A method according to Claim 1, further comprising adding a base.

10. A method according to Claim 9, wherein said base is sodium hydroxide.

11. A method according to Claim 1, wherein said tonicity adjuster is selected from the group consisting of glycerin, sorbitol and dextrose.

12. A method according to Claim 11, wherein said tonicity adjuster is sorbitol.

13. A method according to Claim I, wherein the molar ratio of said acid to said 1-isobutyl-1H-imidazo-[4,5-c]quinolin-4-amine or 1-(2-hydroxy-2-methylpropyl)-1H-imidazo[4,5-c]quinolin-4-amine is between about 0.5/1 and 20/1.

14. A method according to Claim 13, wherein the molar ratio of said acid to said 1-isobutyl-1H-imidazo-[4,5-c]quinolin-4-amine or 1-(2-hydroxy-2-methylpropyl)-1H-imidazo[4,5-c]quinolin-4-amine is between about 1/1 and 4/I.

15. A method according to Claim 1, wherein the osmolality of said solution is between about 270 and 310 mOsm/kg.

European Patent Office

EUROPEAN SEARCH REPORT

Application Number

EP 90 30 4182

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
Y,D	US-A-4 689 338 (J.F. GERSTER et al.) * Column 1, line 61 - column 2, line 55; column 4, lines 17-19; column 7, lines 50-60; column 33, lines 50-55 *	1-15	A 61 K 31/47 A 61 K 9/08
Y	EP-A-0 219 784 (BAYER AG) * Page 2, line 4 - page 4, line 8; page 4, line 21 - page 5, line 4; page 5, lines 26-30; page 8, line 28 - page 10, line 20; pages 15-20, examples 1,2,3,7,12; claims 1-4 *	1-15	
Y,D	US-A-4 640 930 (E. MOHACSI et al.) * Column 1, lines 1-28; column 8, lines 22-34; column 12, lines 23-39; columns 21,21, example 25 *	1-15	

TECHNICAL FIELDS SEARCHED (Int. Cl.5)

A 61 K

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	03-08-1990	BOULOIS D.J-M.

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
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